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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

BTG INTERNATIONAL LIMITED, et al., Plaintiffs, v. AMNEAL PHARMACEUTICALS LLC, et al., Defendants.	Hon. Kevin McNulty, U.S.D.J. Civil Action No.: 2:15-cv-05909-KM-JBC
BTG INTERNATIONAL LIMITED, et al., Plaintiffs, v. AMERIGEN PHARMACEUTICALS, INC., et al., Defendants.	Hon. Kevin McNulty Civil Action No.: 2:16-cv-02449-KM-JBC
BTG INTERNATIONAL LIMITED, et al., Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Hon. Kevin McNulty Civil Action No.: 2:17-cv-06435-KM-JBC

PLAINTIFFS' POST-TRIAL RESPONSE BRIEF

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page

Cases

Statutes and Regulations

INTRODUCTION

At trial, Janssen[1] proved that Defendants are liable for induced infringement because their proposed labels instruct physicians to perform every step of the method claimed in the '438 patent. Defendants respond with two main arguments. First, they attack the clinical evidence that prednisone has an anti-cancer effect when combined with abiraterone, while ignoring that the scientific community regarded this clinical evidence as valid and significant well before this litigation. Their attacks also mischaracterize and misinterpret the clinical evidence itself. Second, Defendants are wrong on the facts and the law in asserting they cannot induce infringement as a matter of law because FDA supposedly has not approved prednisone for anti-cancer effects.

Defendants' invalidity case fares no better. Defendants did not prove even the threshold requirement that a skilled artisan in 2006 would have been motivated to pursue abiraterone when, to that point, the predominant view was that advanced prostate cancer was hormone-independent, no secondary hormonal therapy had shown survival benefits, scores of other therapies were in development, and abiraterone itself had been abandoned after a phase I trial. Defendants likewise failed to prove a motivation to combine abiraterone and prednisone. They largely abandon the very prior art combinations they agreed to be limited to, repeatedly mischaracterize the prior art, ignore contradictory teachings, and fail to address that their own witnesses dismissed two of their three alleged motivations out of hand. They also virtually ignore the "expectation of success" prong of the obviousness inquiry and fail to refute the objective, real-world indicia that the invention was far from obvious. Defendants thus do not come close to proving obviousness by clear and convincing evidence.

[1] "Janssen" collectively refers to Plaintiffs BTG International Limited, Janssen Oncology, Inc., Janssen Biotech, Inc., and Janssen Research & Development, LLC.

ARGUMENT

I. Defendants Cannot Avoid Induced Infringement of the '438 Patent.

A. Physicians Who Follow Defendants' Proposed Labels Will Directly Infringe the '438 Patent.

Defendants' sole response to the fact that physicians who follow Defendants' proposed labels will directly infringe the asserted claims is the assertion that prednisone does not have anti-cancer effects when administered in combination with abiraterone. Janssen Br. 9-10. But far more than a preponderance of the evidence establishes that prednisone has such effects, as explained in Janssen's opening brief. *Id.* at 10-22. In arguing otherwise, Defendants fail to rebut much of Janssen's proof, mischaracterize the record, omit inconvenient facts, and ignore this Court's claim construction.

1. Defendants Fail to Refute that the Extension Study Demonstrates that Prednisone, in Combination with Abiraterone, Treats Prostate Cancer.

As Janssen's opening brief explained, the COU-AA-001 extension study establishes that prednisone, in combination with abiraterone, treats prostate cancer. Janssen Br. 10-13. Before the extension study, it was unheard of for two drugs that failed separately to succeed together. Janssen Findings of Fact ("JFF") 1052-1054. The extension study defied these expectations by confirming Dr. de Bono's hypothesis that prednisone could reverse resistance to abiraterone and provide a "sustained and durable" anti-cancer effect, as reflected not just in PSA declines, but also in time to PSA progression ("TTPP"), lab tests, scans, and patient symptoms. JFF 95-146.

Defendants dispute the significance of the extension study through the testimony of Drs. McKeague and Mega. But, tellingly, Defendants fail to address the evidence that oncology researchers with no stake in this litigation regarded the extension study's results as both valid and significant. Defendants offer no response to Dr. Ballman's testimony that the *Journal of Clinical Oncology* ("*JCO*"), one of the most influential publications in the field of cancer

research, would not have published *two* articles reporting the results (Attard 2008 and Attard 2009) if its team of clinical and statistical reviewers thought the data were invalid or insignificant.[2] JFF 167-181. Those articles unequivocally report that a glucocorticoid, dexamethasone, "reversed resistance in 33% of patients," JTX 8086 at 3742, and "resulted in successful salvage" of patients whose disease had begun to progress on abiraterone alone, JTX 8083 at 4568-69. Nor do Defendants address testimony from Dr. Charnas and Dr. de Bono that, based on the extension study's efficacy results, Cougar amended the COU-AA-002 phase II protocol and designed the COU-AA-004 phase II study and the pivotal COU-AA-301 phase III study to require administering the combination therapy from the start. JFF 150-151, 163-166; *see also* DTX 1709 at 24:3-24:7, 50:14-51:9. These decisions provide clear and unrebutted evidence of the great weight accorded to the extension study in the real world.

Ignoring this, Defendants contend that the extension study results were merely "anecdotal," not indicative of anti-cancer effects, and ultimately "far short of validated data supporting direct infringement." Defs. Br. 11-14. Even on their own terms, these arguments fail.

a. The Extension Study Results Were Not Anecdotal.

To show that the results are anecdotal, Defendants stress that of the 11 patients in the extension study who had previously progressed on both abiraterone and dexamethasone monotherapies, only four experienced PSA declines greater than 50 percent. *Id.* at 12. There are two problems with this argument. First, it omits a second group of patients in the study, who had progressed on abiraterone monotherapy but were dexamethasone-naïve. JFF 127, 131. In this

[2] Dr. McKeague speculated that the extension study results published in online appendices to the Attard references were "likely" not peer-reviewed. Defendants' Findings of Fact ("DFF") 60. But Dr. Ballman, a deputy editor of *JCO* with firsthand knowledge of its review procedures, testified that all material published by *JCO*, whether online or in print, is peer reviewed the same way. JFF 168, 197-198.

group of 19, six patients had PSA drops of at least 50 percent, JFF 131-132—results that, as Dr. Rettig testified and Defendants do not rebut, supported Dr. de Bono's hypothesis as well, Tr. 645:15-25, 704:3-11. It is therefore Defendants who rely on just a subset of patients in the extension study, whereas Janssen relies on the overall results.[3] JFF 192; *contra* Defs. Br. 11-12; DFF 59.

Second, Defendants ignore that a response rate must be evaluated against baseline expectations, not in a vacuum. When researchers expect *zero* response, given the failure of abiraterone and dexamethasone individually, a *30-plus percent* response rate is quite significant. JFF 133, 189, 192, 1052-54; Tr. 1096:1-1098:9. Moreover, multiple articles corroborate that the extension study validated Dr. de Bono's hypothesis. JFF 159-161. To quote just one, Sartor 2011 wrote that "[t]o reverse resistance to abiraterone" in the extension study, "low-dose steroids *were successfully used* to decrease production of ACTH and upstream steroids at disease progression on abiraterone alone."[4] PTX 344 at 1495 (emphasis added); *see* JFF 162. And, as noted, the extension study's publication in *JCO* and influence on Cougar confirm that its results were truly significant.[5]

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[3] These results were depicted in the waterfall plot in Attard 2009. JFF 134-135. Defendants suggest that the scale of the y-axis is "kind of misleading, or deceptive even" because it cuts off at 25 percent. DFF 73. Dr. Ballman explained, however, that the y-axis stops at 25 percent because a patient whose PSA levels rose by that amount was deemed to have progressed and was removed from the study and placed on a different treatment. JFF 200.

[4] Defendants misleadingly alter testimony from Dr. Mundle to make it appear that he said the de Bono hypothesis would never be considered validated without a phase III study. Defs. Br. 13. In fact, his testimony concerned the effects of prednisone *monotherapy* discussed in an article he co-authored. DTX 1710 at 129:11-130:8; *see* DTX 1215.8.

[5] The extension study also belies Defendants' assertion that Janssen has never tested abiraterone monotherapy against the combination of abiraterone and a glucocorticoid in a single test. *See* Defs. Br. 14. As Janssen demonstrated, each patient in the prospectively designed study served as his own control. JFF 105. Defendants fault this study design for not performing unspecified modeling to address variation in the results, Tr. 940:2-24, but they elsewhere acknowledge that for PSA levels, what matters is overall "trends … because there is variability in the assays used

b. The Extension Study Demonstrated that Glucocorticoids Have Anti-Cancer Effects with Abiraterone.

Defendants next argue that the PSA declines observed in the extension study "do not necessarily translate to anti-cancer effects" and that the extension study "did not … otherwise assess whether dexamethasone … has anti-cancer effects." Defs. Br. 12-13. Neither of these claims is correct. First, it is undisputed that PSA declines of at least 50 percent are a standard criterion for measuring response to prostate cancer therapies. JFF 130. Second, while there may be problems with overreliance on PSA drops in general, Xu 2015, an article published in the prestigious journal *Clinical Cancer Research*, reports that PSA declines of at least 50 percent "were highly associated with [overall survival]" in patients treated with abiraterone and prednisone—evidence Defendants never address. JFF 215-217. Third, even if PSA drops in isolation can be unreliable indicators, here Dr. de Bono validated the PSA data from the extension study by confirming that it corresponded to anti-cancer benefits observable in patients' scans, blood tests, and symptoms. JFF 113. Defendants ignore this testimony from Dr. de Bono, as well as Dr. Mega's acknowledgement that Dr. de Bono's approach to determining therapeutic effectiveness "represents an appropriate standard of care." *Id*. Finally, Defendants omit that the extension study "otherwise assess[ed]" the anti-cancer effects of dexamethasone by measuring TTPP, which was approximately 150 days longer for patients on the combination therapy than for those on abiraterone alone. JTX 8086 at 3745-46. TTPP is highly correlated with overall survival in patients receiving abiraterone plus prednisone, and the longer TTPP observed in the extension study is thus further evidence that glucocorticoids have anti-cancer effects with abiraterone. JFF 215-218.

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to test PSA," DFF 518; JFF 124. Defendants also fail to rebut Dr. Ballman's testimony that she has applied this same study design as an editor and peer-reviewer. JFF 105.

Defendants also suggest that the extension study did not show anti-cancer effects because it did not measure overall survival. Defs. Br. 13. It is undisputed, however, that PSA responses and TTPP, which the extension study did measure, are highly associated with overall survival in patients treated with abiraterone plus prednisone. JFF 215-217. For that reason, the PSA and TTPP improvements in the extension study are indirect evidence of a survival benefit. Regardless, as Defendants concede, a survival benefit is not necessary under the Court's claim construction. *See* Defs. Br. 54. Janssen has shown that 10 mg/day of prednisone satisfies the "therapeutically effective" limitation by proving that, in combination with abiraterone, prednisone contributes to the "eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer." JFF 60. Irrespective of survival benefits, the extension study provides evidence that prednisone, when combined with abiraterone, treats prostate cancer by depriving it of the upstream steroids that fuel its growth. JFF 92-182. Neither Defendants nor their experts have ever advanced another explanation for the extension study's results.

c. The Extension Study Demonstrated an Anti-Cancer Class Effect of Glucocorticoids.

Finally, Defendants are mistaken in arguing that the extension study provides no evidence of *prednisone*'s anti-cancer effects because the study involved *dexamethasone*. Defs. Br. 13-14. Janssen proved that dexamethasone's suppression of upstream steroids in the extension study is a "class effect" common to all glucocorticoids, including prednisone. JFF 138-144. The two drugs are therefore interchangeable for this purpose—a point Defendants' expert Dr. Bantle conceded. JFF 145–146. It is also undisputed that physicians "know the relative potencies of dexamethasone and prednisone" and that 0.5 mg of dexamethasone, the dose used in the extension study, is biologically equivalent to 3.3 mg of prednisone. Tr. 2023:11-25. The

extension study results therefore *do* translate to prednisone, and 10 mg of prednisone does provide anti-cancer efficacy with abiraterone, just as dexamethasone did.[6]

2. Defendants Fail to Refute that the Attard 2009/Ryan 2011 Cross-Study Comparison Further Demonstrates Prednisone's Anti-Cancer Effects.

As demonstrated at trial, Dr. Rettig's cross-study comparison of Cougar's phase II abiraterone monotherapy study (Attard 2009) and phase II combination therapy study (Ryan 2011) provides further evidence of prednisone's anti-cancer effects. Janssen Br. 13-14. Defendants' primary criticism of the cross-study comparison is that it *is* a cross-study comparison, and not a single, multi-armed trial. Defs. Br. 15-16. But Defendants offer no rebuttal to Dr. Ballman's testimony that cross-study comparisons are "very common … especially [for] early phase studies," and allow researchers to interpret the "scientific knowledge known to date." Tr. 1086:11-19; JFF 232. In particular, they offer no explanation why researchers would widely use this approach if it did not yield valid conclusions.[7]

Defendants' more specific attacks on the cross-study comparison are also unavailing. First, Defendants repeat Dr. McKeague's assertion that Dr. Rettig "omits contradictory data" and "does not account" for differences in the studies' designs. Defs. Br. 16-17. As demonstrated, however, this charge is false. *See* Janssen Br. 19-22. Dr. Rettig addressed every piece of

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[6] For this reason, Defendants are wrong to suggest that the LATITUDE study demonstrates that Janssen does not believe that prednisone has anti-cancer effects because the study uses 5 mg/day of prednisone instead of 10 mg/day. Defs. Br. 18. In potency terms, 5 mg/day of prednisone is still greater than the amount of dexamethasone used in the extension study. JFF 514.

[7] Contrary to Defendants' claim (at 16), Dr. Rettig did not testify that cross-study comparisons are entitled to "little weight." That testimony concerned retrospective chart reviews like Sartor 1998, in which researchers pluck records of patients who were not part of any prospective study, and thus may have been treated and managed differently. JFF 805-806. Cross-study analyses, by contrast, compare results across protocol-driven, prospectively-designed clinical trials. To the extent such comparisons are less robust than large randomized, controlled studies, Defendants do not actually identify any such studies calling Dr. Rettig's analysis into doubt.

evidence Defendants accuse him of ignoring, and rather than "blindly conclud[ing] that they don't affect his analysis," Defs. Br. 17, he gave reasoned explanations why they do not invalidate the cross-study comparison. JFF 250-263, 269-304. Instead of explaining why those reasons are wrong, Defendants just persist in mischaracterizing Dr. Rettig's testimony.

Defendants resort to this tactic because they lack evidence that the differences between the studies are clinically significant. As Dr. McKeague conceded, he lacks the expertise to say whether any of the differences he identifies matters clinically. JFF 283-84, 287, 292, 296. Such judgments must be made by a clinician, JFF 284, and Defendants' clinical expert, Dr. Mega, failed to address all but one of the differences.[8] As a result, Defendants can only speculate that the differences "could have" mattered, Defs. Br. 17, which is non-responsive to Dr. Rettig's explanations why, in fact, they do not matter. *See* JFF 250-263. Furthermore, Defendants offer no rebuttal to Dr. Rettig's testimony that the Attard 2009 and Ryan 2011 patients were essentially identical across numerous important prognostic factors, which validates the cross-study comparison. JFF 230-249, 304; *see* Janssen Br. 22.

Second, Defendants contend that the difference in TTPP observed in the cross-study comparison lacks statistical significance because the 95-percent confidence intervals overlap. Defs. Br. 17. Defendants, however, do not dispute Dr. Ballman's testimony that 90-percent

[8] The one difference Dr. Mega addressed—in baseline PSA levels—was beyond the scope of his expert reports and should be stricken on that basis. *See* Janssen Br. 15-16. Regardless, Defendants do not actually rely on this testimony from Dr. Mega, *see* Defs. Br. 16 (citing DFF 80), and Dr. Rettig explained why the difference is not clinically significant, JFF 252. Defendants attempt to undermine Dr. Rettig's explanation by noting that he regarded a PSA decline of similar magnitude to the difference in baseline PSA levels as clinically significant. Defs. Br. 16. But this criticism misrepresents how PSA endpoints are measured. It suggests that absolute numbers matter, when in fact it is *percentage* declines that are important. *See, e.g.*, JTX 8083 at ZYTIGA_04501727 (measuring PSA decline in percentage terms); JTX 8086 at 3743 (same); JTX 8093 at 4856 (same).

confidence intervals likely would not overlap here, and are commonly used in phase II cancer studies. JFF 314-317. A 90-percent likelihood that TTPP on the combination therapy is longer than on abiraterone monotherapy is clearly sufficient under a preponderance standard. Similarly, Defendants do not dispute that the scholarly literature recognizes a rule of thumb that 95-percent confidence intervals would have to overlap by more than 25 percent before the P-value exceeded 0.05, or that the intervals in Attard 2009 and Ryan 2011 overlap by less than ten percent. JFF 319-329. Their only response is to cite a boilerplate cautionary statement that this rule of thumb is not intended to replace statistical calculations or to give precise P-values. Defs. Br. 17 n.3; *see* Tr. 1101:6-11. But Defendants offer no critique showing that the peer-reviewed methodology Dr. Ballman relied on is unreliable to establish that the median TTPP value in Ryan 2011 is statistically significantly greater than the median TTPP value in Attard 2009, even at the 95% level of confidence Defendants demand.[9] JFF 319-329.

Given the dearth of evidence supporting their criticisms of the cross-study comparison, Defendants invoke the PTAB decisions. Defs. Br. 16. But the PTAB ruled based on a paper record from Dr. McKeague, without the benefit of any expert rebuttal, as Drs. Ballman and Rettig provided here, because Defendants submitted Dr. McKeague's analysis to the PTAB only in connection with their reply brief. As a result, the PTAB lacked the two things—Drs. Ballman and Rettig's rebuttal testimony and Dr. McKeague's live-cross examination—that have now exposed Dr. McKeague's criticisms of the cross-study comparison as unfounded, speculative, and sloppy. *See* Janssen Br. 19-21 & nn.7-9. The PTAB's ruling deserves no weight.

[9] Defendants assert that "[s]tatistical significance cannot be drawn when data has overlapping confidence intervals unless a hypothesis test was performed." Defs. Br. 17 (citing DFF 80). Their proposed finding, however, cites no evidence supporting this assertion; it does not even discuss hypothesis tests. JFF 318-329.

Finally, Defendants attempt to refute both the extension study and cross-study comparison by pointing to various articles that purportedly proclaim an "absence of data" supporting prednisone's anti-cancer efficacy. Defs. Br. 14, 17-18. But Defendants elide the fact that none of the articles examined whether prednisone has anti-cancer effects *in combination with abiraterone*. As Dr. Mega conceded, Sonpavde 2016 focused only on prednisone monotherapy, and "did not look at [prednisone] in combination with abiraterone." JFF 378-379. The same is true of Morgan 2014. DTX 1573.2. And studies such as Gill 2017,[10] which evaluated the use of abiraterone without prednisone, confirm that abiraterone can be safely administered without prednisone, but fail to rebut Janssen's proof of prednisone's anti-cancer effect with abiraterone. JFF 515. Indeed, the recent abiraterone monotherapy study Defendants cite provides for adding prednisone upon disease progression, as in Dr. de Bono's dexamethasone extension study, reflecting the belief that adding prednisone contributes efficacy even where abiraterone alone has failed. DTX 1712. Defendants ultimately have no evidence that prednisone does *not* have anti-cancer effects in combination with abiraterone, let alone evidence sufficient to rebut Janssen's showing that it does.

B. Janssen Proved that Defendants Will Induce Infringement Because Their Proposed Labels Affirmatively Instruct Physicians to Carry Out the Infringing Method.

The conclusion that Defendants induce infringement inescapably follows the determination that physicians will directly infringe the '438 patent by administering 10 mg/day of prednisone with 1000 mg/day of abiraterone to prostate cancer patients. Janssen Br. 22-24. In a Hatch-Waxman case, a defendant induces infringement if its "proposed label instructs users to

[10] Contrary to Defendants' assertion (at 18), Gill 2017 is a completed, retrospective analysis of selected patients, and it was not sponsored by Janssen. *See* DTX 1571.

perform the patented method." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). Such a label establishes both active steps and specific intent to encourage inducement. *See Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1369 (Fed. Cir. 2017); *Takeda Pharm. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 630 (Fed. Cir. 2015). Here, physicians will practice the '438 patent by (i) administering abiraterone in combination with prednisone (ii) to patients with mCRPC (iii) in dosages of 1000 mg/day and 10 mg/day, respectively. JFF 454. And that is precisely what Defendants' labels instruct physicians to do. JFF 453-457; *e.g.*, PTX 359 at AMN-ABIRA-0064217.

1. Defendants' Labels Encourage Direct Infringement of the '438 Patent.

Defendants nevertheless contend that their labels do not actively encourage infringement because the labels supposedly do not "encourage[] doctors and patients to use prednisone to fight cancer, as opposed to addressing abiraterone side effects." Defs. Br. 27. Even if this description of the labels were true—and it is not, *see infra* at 13-15—it is legally irrelevant. As Defendants conceded, a physician's subjective intent in administering prednisone "is absolutely irrelevant to direct infringement." Tr. 62:3-4. Therefore, to actively encourage direct infringement, Defendants' labels need not teach any specific reason for giving prednisone. They simply need to instruct physicians to practice every step of the patented method—which they do.

Defendants cannot escape this conclusion by claiming that their labels "[m]erely describe[e]" or "permit" an infringing use, rather than encourage it. Defs. Br. 28-29. None of the cases they cite is factually analogous to this one. In *Acorda Therapeutics Inc. v. Apotex Inc.*, the patent covered methods of administering tizanidine with food to reduce tizanidine-induced drowsiness. 2011 WL 4074116, at *1 (D.N.J. Sept. 6, 2011). The defendant's label, however, "d[id] not direct a physician or patient to administer the [tizanidine] capsules with food," and the statements the plaintiff relied upon to show inducement did not "direct any action on the part of

any physician." *Id.* at *17. In *In re Depomed Litigation*, the patent covered the use of a drug for polyneuropathic pain, but the defendant's label "only instruct[ed] the user to administer the drug to treat severe chronic pain," a different condition afflicting different patients. 2016 WL 7163647, at *63 (D.N.J. Sept. 30, 2016). Thus, the court found that the defendant's label did not include instructions that "*would necessarily lead*" to the infringing use. *Id.* at *64. And in *Shire LLC v. Amneal Pharmaceuticals, LLC*, the patent covered use of a drug *with* food, but the defendant's label was "indifferent" to whether the drug was taken with or without food. 2014 WL 2861430, at *5 (D.N.J. June 23, 2014). The court found that the "proposed label does not contain any instruction to take the medication with food." *Id.* Thus, in each of these cases, the label did not affirmatively instruct physicians to perform some essential step of the patented method.

Here, by contrast, Defendants' labels teach exactly one use of abiraterone and prednisone, and that use is infringing. The labels list one indication for abiraterone and prednisone and one "[r]ecommended dose," *e.g.*, PTX 359 at AMN-ABIRA-0064217, and, when followed, those instructions will "*necessarily lead*" to direct infringement. *In re Depomed*, 2016 WL 7163647, at *64; *see* JFF 394-397. Accordingly, Defendants' labels permit no non-infringing use. Because Defendants' labels instruct only "how to engage in an infringing use," they constitute "active steps … to encourage direct infringement." *Takeda*, 785 F.3d at 630-31.

2. Defendants' Labels Establish Specific Intent to Encourage Infringement.

Defendants also contend that their labels do not support an inference of specific intent because the use claimed in the '438 patent supposedly is not FDA-approved. Defs. Br. 19-27. This argument fails for three independent reasons.

First, the Federal Circuit has held that "evidence that the product labeling that Defendants

seek would inevitably lead some physicians to infringe establishes the requisite intent for inducement." *Eli Lilly*, 845 F.3d at 1369. Here, Janssen has shown that Defendants' proposed labels would inevitably lead *every* physician to infringe. Janssen Br. 22-24; *supra* at 10-11. Physicians will infringe the '438 patent *every* time they follow Defendants' instructions. This establishes specific intent as a matter of law.

Second, Defendants are mistaken that inducement requires the FDA to have approved prednisone for anti-cancer effects. The requirement of FDA approval is not part of a traditional infringement analysis under 35 U.S.C. § 271(b), but rather is an artifact of § 271(e)(2). *See Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1354-62 (Fed. Cir. 2003) (deriving the requirement of FDA approval from the text of § 271(e)(2), and analyzing that provision separately from § 271(b)). As Janssen demonstrated, § 271(e)(2) requires FDA approval only of the use of the drug *that is the subject of the ANDA* (here, abiraterone), not any concomitant medication (here, prednisone). *See* Janssen Br. 24-25; *see also Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1324 (Fed. Cir. 2003) (per curiam) (explaining the inducement analysis in *Allergan* is limited to circumstances in which, *inter alia*, "the ANDA applicant seeks approval for the production of a generic version of *the drug* for a use that is different from the method of use of the drug that is claimed in the patent" (emphasis added)). Here, regardless of the precise role FDA understood prednisone to play, it is undisputed that FDA approved abiraterone for use in combination with prednisone to treat cancer. Defendants' ANDAs, which seek approval for this use of abiraterone, thus constitute "act[s] of infringement" under § 271(e)(2).

Finally, even if FDA approval of prednisone's anti-cancer role were necessary, Defendants fail to refute that the ZYTIGA labels—and, therefore, Defendants' labels—reflect such approval. According to Defendants, the FDA approved prednisone only to treat

abiraterone's side effects. Defs. Br. 21-22. But as Janssen demonstrated, FDA regulations preclude this interpretation of the Indications and Usage section of the ZYTIGA label. Janssen Br. 27. Those regulations make no provision for indications related to side effects of medication. *See* 21 C.F.R. § 201.57(c)(2). Thus, as both sides' regulatory experts agreed, prednisone would "not be there in the indications and usage section … if it is there for side effects." JFF 533-538. As Janssen established, under § 201.57(c)(2), the only viable interpretation of the Indications and Usage section is that abiraterone and prednisone are approved, together, to treat mCRPC. Janssen Br. 26-27; JFF 521-552. In other words, even if the Court agrees that the Indications and Usage section is "vague," as Defendants contend (at 19-20), FDA regulations rule out all but Janssen's interpretation.[11]

Defendants fall back on the argument that FDA could not have approved prednisone for anti-cancer effects because no adequate and well-controlled studies provide "substantial evidence" that prednisone has such effects. Defs. Br. 23. But Defendants' view that FDA approved prednisone to manage mineralocorticoid excess caused by abiraterone is vulnerable to the same objection: Defendants have not identified any adequate and well-controlled studies supporting this use of prednisone in this patient population either. *See* JFF 540. The fact is that FDA approved prednisone to treat prostate cancer only as part of a combination therapy with abiraterone, and thus required only substantial evidence that the *combination* is safe and effective for that purpose. Janssen Br. 28-29; JFF 569-570. It is undisputed that the COU-AA-301 and COU-AA-302 studies provided that evidence, and it is further undisputed that FDA would have interpreted those studies in light of the earlier studies demonstrating prednisone's anti-cancer

[11] Defendants cite the labels of Jevtana and Taxotere (docetaxel), two different drugs in a different pharmacological class. But those labels do not change the plain text of 21 C.F.R. § 201.57(c)(2), and thus have no bearing on the meaning of the ZYTIGA label here.

efficacy.[12] FOF 561-568. Thus, as reflected in the Clinical Studies section of ZYTIGA's label, the FDA agreed that Janssen's phase III studies demonstrate "[t]he efficacy and safety of ZYTIGA *with prednisone*," not the efficacy of ZYTIGA alone.[13] JFF 561 (emphasis added).

While irrelevant, Defendants have selectively quoted the FDA "approval package" materials. Defendants ignore, for example, the statement in the 2012 FDA approval package that "[a]biraterone acetate *in combination with prednisone* has been approved for the treatment of metastatic CRPC." DTX 1340.235-236 (emphasis added). They similarly omit that the Summary of Clinical Efficacy repeatedly describes the efficacy of abiraterone *and* prednisone,[14] and that the ZYTIGA approval package describes COU-AA-001 and COU-AA-002 as "supportive efficacy trials," DTX 1340.284.[15]

Ultimately, Defendants fail to refute that the ZYTIGA label embodies FDA approval of abiraterone and prednisone, in combination, for treating mCRPC.[16] Numerous statements in the

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[12] Defendants suggest the Kaplan-Meier curves in the Clinical Studies section attribute efficacy to abiraterone alone. DFF 234. But Dr. Mega conceded that the curves show the efficacy of abiraterone and prednisone in combination. Tr. 1240:3-13. Other statements in the Clinical Studies section likewise attribute efficacy to the combination. JFF 480-487.

[13] Contrary to Defendants' suggestion (at 24-25), Janssen markets ZYTIGA and prednisone, not ZYTIGA alone, as effective against mCRPC. JFF 636-643. Even Dr. Mega conceded that he has reviewed Janssen literature promoting the combination as efficacious. JFF 639.

[14] *See, e.g.*, JTX 8187 at 9; *id.* at 7.

[15] Defendants also rely on Dr. Charnas's testimony that Janssen did not ask FDA specifically to approve prednisone for its anti-cancer effect. Defs. Br. 21. Dr. Charnas, however, was referring to approval for a prednisone tablet, which Janssen does not market. He testified that while Janssen did not seek approval for a new indication on a prednisone label, it sought marketing authorization for ZYTIGA, to be used with prednisone, and that the combination is what showed the anti-cancer efficacy. Tr. 309:21-310:3, 310:20-311:2, 370:6-16.

[16] Defendants suggest that approving prednisone in combination with abiraterone would represent a "sudden[] change[of] course" for the FDA, which has never approved prednisone alone to treat cancer. Defs. Br. 19. But Defendants do not rebut Dr. Rettig's testimony that, with cancer therapies especially, it is common for two drugs to be approved in combination when neither is approved as a standalone therapy. JFF 541-542.

Indications and Usage, Dosage and Administration, and Clinical Studies sections speak to this purpose. JFF 527-530, 558-559, 561-568. By contrast, Defendants fail to identify *any* language in the label instructing physicians to give prednisone for abiraterone's side effects. *See generally* JFF 463-509, 519-570, 590-611.

3. Defendants Satisfy the Knowledge Element of Inducement.

As a last-ditch effort to avoid inducement, Defendants contend that Janssen did not prove that they know infringement will occur if their ANDAs are approved. Defs. Br. 31. It is black letter law, however, that under Hatch-Waxman, knowledge is assessed at the time of FDA approval. *See Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 643 (Fed. Cir. 2017). Thus, if the Court finds (as it should) that 10 mg/day of prednisone is "therapeutically effective" and that physicians will directly infringe the '438 patent if Defendants' ANDAs are approved, Defendants will indisputably know that infringement will occur from marketing their abiraterone products.

II. Defendants Cannot Avoid Contributory Infringement of the '438 Patent.

Janssen's opening brief also demonstrated that Defendants will contribute to infringement of the '438 patent. Janssen Br. 33-34. Defendants contest only two elements of this claim. First, they contend that their abiraterone products are not "especially made" for an infringing use because they are "made solely for the FDA-approved use, which is not the patented use." Defs. Br. 32. As Janssen has now repeatedly shown, however, the FDA-approved use *is* infringing. *See* Janssen Br. 33; JFF 696-697; *see generally* JFF 386-449.

Second, Defendants contend their products are suitable for substantial non-infringing uses. Defs. Br. 32-33. But the uses they identify do not qualify for this safe harbor. The "use [of abiraterone] with prednisone for glucocorticoid replacement," *id* at 32, is still infringing because, as Defendants concede, a physician's reason (*i.e.*, intent) for giving prednisone is irrelevant to

direct infringement.[17] *Supra* at 11; *see* JFF 707-709. The "use of abiraterone with no prednisone at all," *id.* at 33, meanwhile, is off-label and therefore not a substantial non-infringing use as a matter of law. *See Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 927 (Fed. Cir. 2011); JFF 711-713, 717-719. The record, moreover, uniformly indicates that use of abiraterone monotherapy is exceedingly rare, not substantial. JFF 714-716, 719. Finally, Defendants suggest that because prednisone has anti-cancer effects only in *some* patients, its use in patients who do not experience these effects is non-infringing. Defs. Br. 32-33. But Defendants adduce no legal support for this position, which, by its logic, would mean that contributory infringement never applies in drug cases because no drug works in every patient. *See* Tr. 388:23-25, 604:14-19. This Court should reject such an extreme and unfounded position.

III. Defendants Failed to Prove Obviousness of the Asserted Claims.

Defendants acknowledge they had the burden to establish obviousness of the asserted claims by clear and convincing evidence—far more than the preponderance standard used by the PTAB. Defs. Br. 34. But they utterly failed to carry it.

A. Defendants Lack Clear and Convincing Evidence that a Person of Ordinary Skill Would Have Been Motivated to Combine Abiraterone and Prednisone for Treatment of Prostate Cancer with a Reasonable Expectation of Success.

As Janssen showed and Defendants failed to rebut, a skilled artisan in 2006 would not have chosen a secondary-hormonal therapy to combat mCRPC, much less have chosen abiraterone and combined it with prednisone. Janssen Br. 37-54. And each of Defendants' three reasons a skilled artisan might combine abiraterone and prednisone also fails.

[17] That prednisone has unclaimed benefits is irrelevant because, as this Court recognized, the '438 patent does not "disclaim[]" such additional benefits. Dkt. 239 at 15. Therefore, prednisone's multiple effects do not change the infringement analysis. *See Vulcan Eng'g Co., Inc. v. Fata Aluminum, Inc.*, 278 F.3d 1366, 1375 (Fed. Cir. 2002); *N. Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 945 (Fed. Cir. 1990).

1. Defendants Lack Clear and Convincing Evidence of a Motivation to Pursue Development of Abiraterone.

Defendants do not dispute that uncertainty and innumerable hypotheses existed in 2006 about the causes of advanced prostate cancer. Nor do Defendants dispute that over 200 compounds were in development for advanced prostate cancer. The responses Defendants do make fail to show a motivation to "pluck[]" secondary-hormonal therapies or abiraterone "out of the sea of prior art." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1337 (Fed. Cir. 2016).

Defendants' principal response is that the existence of their prior art references, such as O'Donnell 2004, itself is evidence that a skilled artisan would pursue secondary-hormonal therapies or select abiraterone. Defs. Br. 56-57. This response, however, ignores that "[e]vidence of obviousness … is insufficient unless it indicates that … skilled artisans would have had reason to select the route that produced the claimed invention." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1072 (Fed. Cir. 2012). Defendants offer no particular reason why a skilled artisan would pursue a secondary-hormonal therapy, much less abiraterone, in the face of numerous hypotheses and options, especially when no other secondary-hormonal therapy had been proven efficacious. Essentially, Defendants' argument is that secondary-hormonal therapies, or abiraterone, were obvious to try. But the Federal Circuit has explained that this "obvious to try" reasoning has merit only "where a skilled artisan merely pursues 'known options' from a 'finite number of identified, predictable solutions.'" *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). "[W]here," on the other hand, "a defendant merely throws metaphorical darts at a board filled with combinational prior art possibilities, courts should not succumb to hindsight claims of obviousness." *Id.* Yet metaphorical darts are all Defendants have here. The mere existence of prior art on abiraterone alone cannot answer *why* a skilled artisan would select secondary-hormonal therapy or

abiraterone among the numerous hypotheses or 200-plus potential therapies for combatting prostate cancer.[18] Nor could they identify or point to a finite number of known or predictable solutions, especially in the face of O'Donnell 2004's conclusion that abiraterone as a secondary-hormonal treatment was an "unproven hypothesis." Tr. 216:6-22; DTX 1129.8.

Defendants next contend they do not need to explain why a skilled artisan would pursue a secondary-hormonal therapy or select abiraterone because the "lead compound" case law is inapplicable here and because traditional obviousness analysis applies. Defs. Br. 57. But *In re Cyclobenzaprine*, *In re Kubin*, *In re Johnston*, *Viiv Healthcare UK Ltd.*, and other cases relied upon by Janssen are not "lead compound" cases, and the principles in them are generally applicable to all obviousness cases.

Beyond that, Defendants merely suggest that a researcher would select abiraterone to treat prostate cancer because abiraterone was "well known." Defs. Br. 35, 56. But even if this were correct (and it is not), this is legally insufficient without any reason why a researcher would select abiraterone among the hundreds of possible drugs to treat prostate cancer. *See In re Cyclobenzaprine*, 676 F.3d at 1072.

Compounding their legally flawed analysis, Defendants mischaracterize what the prior art taught about abiraterone. Defendants tout Barrie 1994, Potter 1995, and Jarman 1998, Defs. Br. 35, but these references described only *in vitro* and animal test data, which are not measures of clinical efficacy and did not suggest that abiraterone would be efficacious in humans. JFF 792;

[18] Defendants assert that O'Donnell 2004 and many other contemporaneous references reflect that second-line hormonal therapies would work for mCRPC. Defs. Br. 55-56. But this is based on an unsupported assertion by Dr. Lipton. Record evidence disproves Defendants' claim, including that no company was interested in abiraterone and that O'Donnell 2004 concluded that, as a second-line treatment, abiraterone was an "unproven hypothesis." Tr. 241:13-24; 216:6-22. Several prior art references in 2006 surveyed the state of the field and nowhere mentioned abiraterone. Janssen Br. 40.

Tr. 1668:14-19, 1875:18-1876:1. Nor did these references reflect a widespread interest in abiraterone. Rather, they were all authored by the inventors of the '213 patent, the same group that tried and failed to license abiraterone for five years. JFF 781, 1030, 1045, 1047.

Defendants contend that Barrie 1994 "acknowledges that prostate cancer progressing after castration was still 'hormone-dependent' and subject to hormonal therapies like abiraterone." Defs. Br. 35 n.9. However, Barrie 1994 was authored 12 years before 2006, and thus pre-dates the failure of other secondary hormone treatments and the conclusions of researchers during the ensuing period.[19] JFF 751-762. Moreover, Barrie 1994 was describing the potential use of abiraterone as a replacement for ADT, not a secondary therapy after progression on ADT (*i.e.*, for mCRPC). DTX 1062.7.

Defendants also highlight the '438 patent's supposed acknowledgement that the '213 patent taught abiraterone might be useful in the treatment of prostate cancer. Defs. Br. 35-36. But the statement at issue was made by the inventors of the patent-in-suit, at a time after they had discovered that abiraterone is efficacious when combined with prednisone. In describing their discovery, they were merely identifying with hindsight the prior art that preceded their work. As the evidence demonstrated at trial, the referenced '213 patent contains only in vitro and pre-clinical data and pre-dates O'Donnell 2004 by almost a decade. JFF 792. If it were obvious from the 1997 '213 patent to develop abiraterone to treat advanced prostate cancer with an expectation of success, surely someone would have done so long before the '438 inventors had their insight. Underscoring this, Defendants' expert Dr. Lipton was aware of abiraterone since

[19] Defendants contend that terms like "androgen-independent" or "hormone-refractory" did not mean a skilled artisan would not be interested in secondary-hormonal therapies, Defs. Br. 56, but that assertion does not withstand scrutiny. Not only did the terms reflect this view, but researchers affirmatively taught away from secondary-hormonal therapies. Janssen Br. 38.

the 1990s but, like others, never attempted to pursue it. JFF 793, 794. Defendants also ignore that the '213 patent described many CYP17 inhibitor compounds, including compounds reported to be more potent than abiraterone. JFF 799; Tr. 1861:23-1864:12. A skilled artisan would have pursued a more potent compound because it was more likely to work. JFF 798. Defendants therefore offer nothing more than hindsight; they provide no evidence for why a skilled artisan would be motivated to select abiraterone.

The centerpiece of Defendants' obviousness case—O'Donnell 2004—does not help Defendants either. Janssen Br. 39-40. Defendants insist that O'Donnell 2004 taught "treatment with abiraterone acetate result[ed] in sustained suppression of the testosterone/androstenedione axis." Defs. Br. 36. This argument, however, focuses on the results of a single dose study and ignores the multi-dose study showing that targeted suppression of testosterone was not reached. DTX 1129.5; Janssen Br. 39. In fact, at the doses tested, abiraterone failed to achieve sustained testosterone suppression in any patient tested. JFF 771. Similarly misguided is Defendants' assertion that O'Donnell 2004 would have motivated a skilled artisan to choose 1000 mg/day of abiraterone as a therapeutic dose because O'Donnell 2004 stated that a "dose of at least 800 mg is required to maintain testosterone suppression to target levels." Defs. Br. 36. O'Donnell 2004 was not designed to, and did not, establish abiraterone's clinical efficacy in treating prostate cancer. JFF 768-770. And, a person of ordinary skill reading O'Donnell 2004 would not have known whether increasing the dose of abiraterone beyond 800 mg/day would result in sustained testosterone suppression because the dose-response relationship is not typically linear. JFF 772.

Defendants also contend that Dr. de Bono concluded in Attard 2005 that adrenal testosterone production was the logical target for a new drug, that abiraterone specifically targeted adrenal testosterone production, and that O'Donnell 2004 showed abiraterone

suppressed testosterone production. Defs. Br. 36. However, Attard 2005 merely reviewed O'Donnell 2004, providing no original data. And when read as a whole, Attard 2005 actually stands for the opposite of what Defendants claim. It states that Studies A and B of O'Donnell 2004 showed that abiraterone had no consistent effect on testosterone and did not suppress testosterone levels to targeted levels. JTX 8072 at 1244-45. And it states that O'Donnell 2004's Study C showed that testosterone levels were suppressed for three days, but then reversed, such that "the effect of abiraterone was insufficient to offset the rise in LH." JTX 8072 at 1245. Hence, Attard 2005 concluded that "there is no evidence of clinical efficacy." *Id.*

Defendants also contend that Garnick 2006 teaches that abiraterone was under development as a second-line hormonal therapy for prostate cancer. Defs. Br. 36. But, reporting on O'Donnell 2004, Garnick 2006 actually taught that abiraterone failed to achieve sustained testosterone suppression. DTX 1157.8; JFF 771. Garnick 2006 also taught numerous other investigational hormonal agents with a variety of different mechanisms of action, which were further along in clinical development. JFF 775, 776.

As the Federal Circuit explained in *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853 (Fed. Cir. 2015), the obviousness inquiry cannot simply define the problem in terms of its solution and work through the issue from that vantage point. *Id.* at 859. "Whether a person of ordinary skill in the art would narrow the research focus to lead to the invention depends on the facts," and where, as here, "there were innumerable options" and perceived "better option[s]," there is a lack of clear and convincing evidence supporting obviousness. *Id.* at 860.

2. Defendants Failed to Establish a Clear and Convincing Motivation to Combine Abiraterone with Prednisone.

Even if a person of skill would have selected a secondary-hormonal therapy, and abiraterone in particular, to treat prostate cancer (all real world evidence to the contrary), that

person would not have been motivated to combine abiraterone with prednisone as a combination therapy for the treatment of mCRPC. Janssen Br. 42-54. None of Defendants' motivation theories—for prednisone's anti-cancer effects, for its treatment of abiraterone's side effects, or for palliation—has any merit. Moreover, Defendants cannot meet their heavy burden with abstract arguments. They must rely on the prior art combinations they agreed to limit themselves to at trial. In their post-trial brief, Defendants do not even attempt to do this because they cannot. This is reason alone to rule in Janssen's favor.

a. Defendants' Two Active Anti-Cancer Agents Theory Fails to Establish a Motivation to Combine Abiraterone and Prednisone.

Defendants' theory that a person of ordinary skill would combine abiraterone and prednisone for their individual anti-cancer effects is unsupported. Janssen Br. 42-46. By 2006, abiraterone had not been shown to be efficacious in treating prostate cancer, and Defendants' argument that the prior art was "suggestive" that prednisone provided an anti-cancer benefit is meritless.

Defendants' entire theory is undercut by their expert, Dr. Mega. He testified: "In my view in trying to recall back in 2006, I, as a cancer physician, I did not have any expectations that there was an anti-cancer benefit [with prednisone]." Tr. 1254:24-1255:11. He further explained that he and other physicians had no expectation that prednisone would have a clinical anti-cancer benefit in patients with prostate cancer because "there wasn't any proof of an anti-cancer benefit, so our expectations were diminished." Tr. 1260:10-15. This alone precludes any finding of clear and convincing evidence that prednisone was expected to have anti-cancer effects, or that a skilled artisan would have been motivated to combine prednisone with abiraterone for those effects.

Defendants nonetheless contend Sartor 1998 taught that prednisone could decrease PSA

levels in some patients whose initial hormonal therapy with medical or surgical castration had failed. Defs. Br. 46. But once again, Dr. Mega disagreed. He testified that Sartor 1998 does not show prednisone treats prostate cancer under this Court's claim construction. Tr. 1257:4-1258:7; JFF 818. Moreover, Sartor 1998 itself reported that the magnitude and duration of PSA effects were "modest," JFF 808, and the author of Sartor 1998 later confirmed that prednisone was not expected to have an anti-cancer effect. PTX 108; JFF 819-822. Further, other contemporaneous researchers agreed that the significance of the results of Sartor 1998 was "limited" by the retrospective nature of the study and the small number of patients. DTX 1104; JFF 829.

Defendants respond that Dr. Rettig's reliance on PSA data for infringement purposes is inconsistent with criticism of PSA levels in Sartor 1998. Defs. Br. 48. Not so. As Dr. Rettig explained, researchers knew by 2006 that the PSA data reported in Sartor 1998 for prednisone did not correlate with survival benefit. JFF 833-834. By contrast, later studies analyzing PSA results of abiraterone with prednisone showed the combination resulted in an increased time to PSA progression and an improvement in overall survival. JFF 214-229, 342-372. Context is critical. Tr. 1975:18-1976:6.

Defendants also cite Fossa 2001 to bolster Sartor 1998, even though Defendants have never before offered Fossa 2001 as part of any obviousness combination. Defs. Br. 47. Regardless, Fossa 2001 added nothing to Sartor 1998 and confirmed that prednisone did not improve survival for mCRPC patients. JFF 826-828, 832. And, Oh 2001 summarized the lack of motivation in the field with regard to prednisone at the time: "no study has yet demonstrated a survival benefit with the use of [treatments such as prednisone], which can be expensive as well as toxic, with a potential negative effect on quality of life." JTX 8056 at 91; JFF 824.

Even if there were some suggestion to a skilled artisan that prednisone had some anti-

cancer effect (and there is not), Defendants are also wrong that Vidal 2004 would have instructed a person of skill to combine anti-cancer treatments. *See* Defs. Br. 47. Defendants do not even bother advancing Dr. Lipton's facially implausible notion that there is inherently a motivation to combine any two potential anti-cancer agents. Tr. 1740:1-1741:11; *see* Janssen Br. 44. Defendants recognize that Vidal 2004 emphasizes that combining anti-cancer agents should be "biology-based," Defs. Br. 47-48, but they fail to acknowledge that this further reinforces that a skilled artisan would not have chosen abiraterone and prednisone. As Dr. Rettig explained, Vidal 2004's reference to "biology-based" combinations taught a person of skill to "understand the disease before … start[ing to] throwing drugs at it." Tr. 1939:1-9; JFF 856. Dr. de Bono similarly explained that it is advisable to determine what a drug monotherapy does before considering combinations. Tr. 171:16-172:11; JFF 857. But, in 2006, mCRPC and its causes were little understood, and individual monotherapies for mCRPC were similarly not well understood. JFF 723-733. Accordingly, Vidal 2004 provided no motivation to combine two little understood drugs for a disease that was also not well understood. If anything, Vidal 2004 taught away from using a selective CYP17 inhibitor such as abiraterone and toward the use of a less selective agent in any combination. JFF 855; DTX 1135.6 (expressing "increasing interest in less selective agents that can hit multiple targets"). Defendants have identified no biology based reason to combine abiraterone and prednisone.

Defendants respond to Vidal 2004's discussion of many pathways for new prostate cancer drug development by contending that in the section discussing prostate cancer, Vidal 2004 identified only two ways: "abiraterone and corticosteroids like prednisone." Defs. Br. 48. Defendants ignore that Vidal presented abiraterone and prednisone as alternatives, not candidates for a combination. Janssen Br. 45. Defendants' argument is also premised on a selective reading

of Vidal 2004 and cherry-picking "circulating low-levels of androgens" from among the laundry list of postulated theories for how prostate cancer develops resistance to androgen deprivation therapy. JFF 847. In fact, Vidal 2004 taught that hormone resistant prostate cancer can go through androgen independent action, *i.e.*, through factors unrelated to androgens. JFF 850. And Dr. Lipton admitted that Vidal 2004 included a hypothesis by which corticosteroids such as prednisone could in fact cause prostate cancer growth. Tr. 1730:7-11; JFF 858.

Thus, Defendants' assertion that Vidal 2004 "instructed a [person of skill] to treat advanced prostate cancer with abiraterone and a glucocorticoid," Defs. Br. 48, is simply wrong. Dr. Lipton admitted that Vidal 2004 never mentioned combining abiraterone and prednisone. Tr. 1741:9-11. Nor does Vidal 2004 mention prednisone or combining steroids such as prednisone with abiraterone as a strategy for reversing resistance to androgen deprivation therapy. JFF 853. And to the extent Vidal 2004 describes administrating low doses of steroids or abiraterone, it suggests use of one or the other, not both in combination. JFF 854.

Defendants contend that motivation to combine prednisone for its anti-cancer effects can be derived from Fakih 2002 and Harris 2002 because they posited a mechanism of action for prednisone's anti-cancer effects. Defs. Br. 47. This ignores, however, that in 2006, as Dr. Lipton conceded, several potential mechanisms for prednisone had been postulated, but a skilled artisan would not have known which—if any—were correct. Tr. 1738:10-1739:25. Moreover, to the extent a person of skill thought prednisone's mechanism of action was suppression of adrenal androgens, that was the same mechanism as abiraterone, and combining two drugs with the same mechanism of action would have been inconsistent with what Defendants claim Vidal 2004 taught. In any event, a skilled artisan in 2006 would have been skeptical that suppression of adrenal androgens would be of any benefit to mCRPC patients; by that point, several clinical

trials with several proposed agents (including prednisone)—which were thought to reduce adrenal androgens—had failed to show a meaningful clinical benefit in mCRPC patients. JFF 734-744, 751-762. Hence, this is not a situation, as Defendants contend, Defs. Br. 50, where scientists performed "routine research methods to prove what was already believed to be the case." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1363-64 (Fed. Cir. 2007).

b. Defendants' Side-Effects Theory Fails to Establish a Motivation to Combine Abiraterone and Prednisone.

Defendants also failed to establish a motivation to combine prednisone with abiraterone to treat abiraterone's side effects. Janssen Br. 47-54. For this theory, Defendants relied only on the combination of O'Donnell 2004 and Gerber 1990—the latter reference for its supposed teaching of the use of prednisone to avoid adrenal insufficiency that might result from ketoconazole. Tr. 1533:5-25, 1604:6-1606; Decl. of Amanda Potter, Ex. 1 (July 19, 2018 email from A. Langford to R. Swanson et al.). But Dr. Lipton conceded at trial that the teachings of O'Donnell 2004 are "at odds with what's taught in the Gerber reference." JFF 885. Likewise, Gerber 1990 is nowhere cited in O'Donnell 2004, even though Gerber 1990 was published 14 years earlier. JFF 868. The notion that one of skill reading O'Donnell 2004 would go to Gerber 1990 and find motivation applicable to abiraterone thus strains credulity.

So too with Defendants' more generalized contention that O'Donnell 2004's discussion of ketoconazole and aminoglutethimide would have motivated a skilled artisan to administer prednisone with abiraterone. Defs. Br. 38; *id.* at 39. Defendants leave out a key teaching of O'Donnell 2004 that "the omission of glucocorticoid replacement when treating with aminoglutethimide and ketoconazole has been shown to be safe and effective." DTX 1129.7; JFF 884. Likewise, Defendants ignore the admission of their own expert, Dr. Mega, who acknowledged that when he used ketoconazole, he did so without a glucocorticoid. Tr. 1261:7-

17. Defendants further ignore that O'Donnell 2004's focus on selectivity and specificity of abiraterone compared to ketoconazole or aminoglutethimide would instruct one of skill that abiraterone was designed and intended to be a less toxic adrenal synthesis inhibitor—*i.e.*, one that does not result in adrenal side effects at all. Tr. 1868:23-1869:16; 1918:14-1919:1. The evidence at trial thus refuted Defendants' argument that experience with ketoconazole would have motivated one of skill to use prednisone with abiraterone.

Because Gerber 1990 and ketoconazole fail to provide the needed motivation, Defendants morphed their argument at trial. Now, Defendants' side-effects argument is premised on the notion that O'Donnell 2004 itself, or various prior art references combined with it, taught that "abiraterone would likely cause harmful adrenal side effects—either adrenal insufficiency or mineralocorticoid excess." Defs. Br. 37. In fact, however, the only clinical data available—the study reported in O'Donnell 2004—showed that abiraterone was "very well tolerated and no serious adverse events attributable to treatment were recorded." DTX 1129.6; JFF 888, 923; *see* JFF 926. Moreover, Attard 2005, upon which Defendants rely, and which described O'Donnell 2004, stated that the "available data are encouraging with respect to side-effects." JTX 8072 at 1245. And Garnick 2006, upon which Defendants also rely, similarly confirmed that abiraterone was "well tolerated and non-toxic." DTX 1157.8. Real world evidence reinforces this. Investigators in the two studies right after O'Donnell 2004 chose not to co-administer a glucocorticoid with abiraterone, JFF 949, confirming that a person of skill would not understand the prior art as teaching abiraterone to have adrenal side effects.

Notwithstanding this, Defendants go so far as to contend that abiraterone's adrenal side effects were predicted from the beginning of abiraterone's development and that O'Donnell 2004 anticipated abiraterone would inhibit cortisol production. Defs. Br. 37. But if, as Defendants

contend, adverse side effects were "predicted" before the study, O'Donnell 2004 would not have commenced an abiraterone monotherapy study. Additionally, it is undisputed from O'Donnell 2004 that a skilled person would have known that cortisol levels remained normal in patients given abiraterone up to 800 mg/day for 12 days. JFF 899-901, 905.

Defendants nonetheless contend "the Synacthen test results" in O'Donnell 2004 "revealed that abiraterone administration caused adrenal insufficiency" that would warrant glucocorticoid replacement. Defs. Br. 37-38. But this too is contradicted by O'Donnell 2004, which concluded only that further study was necessary to determine whether a glucocorticoid would be required "at all." DTX 1129.7; JFF 891, 927; Janssen Br. 47-48.[20]

Defendants say that the Harrison's textbook (which is not one of their secondary references) teaches that the Synacthen test is the method for diagnosing adrenal insufficiency and teaches that all patients with adrenal insufficiency should receive hormone replacement. Defs. Br. 42. Defendants ignore, however, that Harrison's is limited to discussing Addison's disease, a disorder that results from the destruction of the adrenals. DTX 1096.29.[21] Abiraterone does not cause destruction of the adrenal glands; abiraterone's effects would thus be reversible. Tr. 1415:10-1416:12, 1471:5-15. Accordingly, the lessons taught from Addison's disease are inapt.

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[20] Defendants focus on the "abnormal" Synacthen test results reported, Defs. Br. 37-38, but the O'Donnell 2004 authors did not define what they meant by "abnormal" Synacthen test results. JFF 910. Nor did O'Donnell 2004 teach whether "abnormal" Synacthen test results were clinically significant. JFF 911, 940. However, O'Donnell 2004 did define what the authors considered to be a cortisol-related toxicity requiring a halt to increased doses of abiraterone used in the study—a dose-limiting toxicity that did not include "abnormal Synacthen test." DTX 1129.3. No such cortisol-related toxicity was observed.

[21] Harrison's supports Dr. Rettig's and Dr. Auchus's explanation that physicians would first identify signs and symptoms of adrenal insufficiency and only if present perform a screening—*i.e.*, Synacthen test. DTX 1096.30. Defendants contend that a "wait and see" approach would have been highly dangerous, Defs. Br. 44, but the real-world evidence is that this is exactly what researchers did following O'Donnell 2004. JFF 949.

Defendants next turn their focus to Attard 2005, another reference not included in their prior obviousness combinations. Defs. Br. 39-40. Defendants claim that Attard 2005 "built upon O'Donnell's warning of abiraterone's likely adrenal side effects" by reference to the abnormal Synacthen tests. Defs. Br. 39.[22] Not only do Defendants ignore Attard 2005's statement that there were "no clinical manifestations of adrenocortical insufficiency" reported in O'Donnell 2004, but Defendants ignore Attard 2005's statement that the available data—*i.e.*, O'Donnell 2004—"are encouraging with respect to side-effects" and that abiraterone was "well tolerated," as well as its explanation that the next clinical studies of abiraterone would not include co-administration with a glucocorticoid. JTX 8072 at 1245.

Despite Attard 2005's affirming the lack of side effects with abiraterone, Defendants assert that Attard 2005 concluded that one of two adrenal side effects would likely occur with abiraterone: adrenal insufficiency or mineralocorticoid excess. Defs. Br. 40-41. In fact, Attard 2005 taught one skilled in the art that even in patients with complete congenital CYP17 deficiency—where patients have no functioning CYP17 enzyme, *i.e.*, they are not making cortisol at all—patients still do not develop adrenal insufficiency because another glucocorticoid, corticosterone, continues to be made and this compensates for the absence of cortisol. *See* JTX 8072 at 1243-44. As Attard 2005 explained, "[s]ynthesis of corticosterone … will not be inhibited by abiraterone and its continued synthesis might prevent clinical manifestations of glucocorticoid insufficiency." JTX 8072 at 1245. So, even if no cortisol were produced with abiraterone (which was known not to be the case), a skilled artisan would not expect adrenal insufficiency to develop based on experience with these complete congenital CYP17 deficient

[22] Defendants assert that Attard 2005 reiterated abiraterone's promising efficacy, Defs. Br. 39, but Attard 2005 states that "there is no evidence of clinical efficacy" with abiraterone. JTX 8072 at 1245; JFF 774.

patients.[23]

Nor does Attard 2005 teach that abiraterone will cause mineralocorticoid excess. Defendants admitted that O'Donnell 2004 does not teach that abiraterone will cause mineralocorticoid excess, Tr. 1408:12-19; JFF 922-926, yet ignore that the only data on mineralocorticoid excess in Attard 2005 would have come from O'Donnell 2004, which Attard 2005 was reviewing. Janssen Br. 50-51.[24]

Defendants are equally wrong that Attard 2005 teaches mineralocorticoid excess must occur from abiraterone if adrenal insufficiency does not. Defs. Br. 40-41. Defendants base their argument on discussions in Attard 2005 about the amount of corticosterone required in the body to compensate for a *complete loss* of cortisol. *See* JTX 8072 at 1243. Attard 2005, as well as O'Donnell 2004, taught one of skill that abiraterone does not cause a complete loss of cortisol, rendering Defendants' assertions inapposite. JTX 8072 at 1243, 1245. And Defendants have offered no evidence on how much of a cortisol reduction a skilled artisan would expect from abiraterone or how much corticosterone would be required to compensate for such a cortisol reduction. JFF 865-867. Moreover, Defendants ignore that Attard 2005 actually presents a third, more likely option—namely, that abiraterone will not cause any side effects requiring

[23] Defendants suggest that Harrison's contradicts this conclusion based on those with lyase deficiency. Defs. Br. 44. But Harrison's does not describe isolated C17,20-lyase deficiency, nor does it group it with the other forms of congenital disorders that Defendants suggest. *See* DTX 1096.32.

[24] Contrary to Defendants' assertion, Figure 1 of Attard 2005 does not teach that mineralocorticoid excess will occur with abiraterone. Defs. Br. 39. Figure 1 shows potential increases and decreases for steroids in the adrenal steroid synthesis pathway, but it does not teach a skilled artisan the precise levels of those increases or decreases. JFF 933. And even if mineralocorticoids did increase with abiraterone, that increase would not necessarily cause a clinical syndrome of mineralocorticoid excess because CYP17 inhibition by abiraterone was known to be incomplete, and because numerous other factors affect steroid synthesis. JFF 934. Researchers in 2006 did not know by how much mineralocorticoids would need to rise in order to result in a clinical syndrome of mineralocorticoid excess. Tr. 1495:16-1497:16.

management because abiraterone may behave more like congenital lyase deficiency—which does not cause adrenal insufficiency or mineralocorticoid excess—than complete CYP17 deficiency. JTX 8072 at 1241-42; JFF 929; Tr. 1897:19-1898:10; *see also* Tr. 1880:4-19.

Defendants say that an FDA endocrinologist reviewing the O'Donnell data confirmed a concern existed that patients taking abiraterone would develop adrenal side effects warranting glucocorticoid supplementation. Defs. Br. 41. But the document referenced by Defendants is not prior art and says nothing about what one of ordinary skill in the art would understand. It is a Cougar document of meeting minutes from a pre-IND meeting, not prior art that could form the basis for an obviousness argument. Moreover, Defendants' reference to "O'Donnell data" is misleading because the document does not cite to or reference O'Donnell 2004 and does not indicate what data the reviewers were considering, much less whether it was publicly available or confidential. In any event, after the pre-IND meeting, FDA as well as Institutional Review Boards approved the protocol for a monotherapy study of abiraterone. JFF 202-205.

The bottom line is that abiraterone does not (and would not be expected to) cause adrenal insufficiency, as noted in Attard 2005. JFF 928-934. Because of this, Defendants were forced to argue that abiraterone would be expected to cause a different problem, mineralocorticoid excess, which is nowhere mentioned in O'Donnell 2004. JFF 922. But even this cannot help Defendants because, as the evidence demonstrated at trial, one of skill still would not co-administer prednisone to manage mineralocorticoid excess, even if it occurred. Symptoms of mineralocorticoid excess are far better handled in other ways. JFF 947-950.[25] That is particularly so in view of the known problems with prednisone. JFF 970-983. These problems

[25] Defendants echo Dr. Bantle's assertion that a physician would not give eplerenone because it might worsen side effects. Defs. Br. 46. Dr. Bantle's assertion was entirely conclusory, lacking support or rationale, and is contradicted by the real-world evidence. JFF 950.

render Defendants' reliance on cases such as *PAR Pharmaceuticals, Inc. v. TWI Pharmaceuticals, Inc.*, Defs. Br. 45, 52, misplaced because those cases find motivation only so long as "the prior art did not teach away." 773 F.3d 1186, 1197-98 (Fed. Cir. 2014). Indeed, if Defendants were correct that the side effects of abiraterone necessitated prophylactic administration of prednisone (and they are not), then in view of the known problems with long term use of prednisone, one of ordinary skill in the art would have had even less incentive to pluck abiraterone out of the "sea of prior art." Defendants' arguments are pure hindsight.

c. Defendants' Palliation Theory Fails to Establish a Motivation to Combine Abiraterone and Prednisone.

Defendants' final motivation to administer prednisone with abiraterone—namely, for palliation—fares no better than its other erroneous theories. Defendants' expert, Dr. Lipton, conceded that a person of ordinary skill would not have looked to Tannock 1996—Defendants' principal prior art reference for palliation—for guidance on what to administer with abiraterone, and he further admitted that palliation would not provide an independent motivation to combine prednisone with abiraterone. Janssen Br. 54-55. Defendants fail to address either of these concessions. That alone is sufficient to dismiss this theory of motivation.

Ignoring all of this, Defendants contend in their post-trial brief that a skilled artisan would have turned to prednisone because it had been FDA-approved for palliative uses. Defs. Br. 51. But prednisone was approved for palliative management of leukemia and lymphomas in adults. Tr. 746:11-13; JTX 8125. It has not been approved for palliation of prostate cancer. As Dr. Nagaich conceded, such a use was—and still is—an off-label use. Tr. 847:2-25. Defendants are equally misleading in asserting that Tannock 1996 acknowledged that corticosteroids provide palliation when used alone or that prednisone's palliative use as a single agent had been a longstanding practice. Defs. Br. 51. Tannock 1996 studied the palliative response of prednisone

as a monotherapy and reported that it resulted in a palliative response in only 12% of patients for a median of 18 weeks. JFF 963. As Dr. Lipton acknowledged, Tannock 1996 would not guide one skilled in the art. JFF 964.

Defendants fall back to generalized assertions about patients suffering from prostate cancer, Defs. Br. 52, but they provide no evidence for why a person of skill would be motivated to provide palliation *with abiraterone*.[26]

B. Defendants Fail to Establish Any Reasonable Expectation that the Claimed Combination Would Effectively Treat Prostate Cancer.

As Janssen explained, even if Defendants could establish a motivation to combine abiraterone and prednisone—and they cannot—they failed to prove that a person of ordinary skill would have had any reasonable expectation of achieving what is claimed by the '438 patent. Janssen Br. 55-58. Defendants do not make any separate showing of a reasonable expectation of success, merely repeating throughout their discussion of motivation that expectation of success would have been reasonable. Defs. Br. 36, 42, 47-48, 51, 55. This is woefully deficient.

A motivation to administer prednisone with abiraterone to treat abiraterone's side effects or palliation cannot establish "a reasonable expectation of achieving *what is claimed* in the patent-at-issue," *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) (emphasis added)—namely, a combination therapy where both drugs are given in amounts that have anti-cancer effects. And as explained, nothing suggested that prednisone

[26] Defendants contend that patients would take glucocorticoids through their secondary cancer treatment, citing as example patients in the -001 study. Defs. Br. 52. But patients in the -001 study received dexamethasone monotherapy because, prior to the '438 patent invention, no other suitable anticancer agents were available. Tr. 158:10-21. Taxotere, mitoxantrone, and Jevtana are all chemotherapy agents, which, Dr. Lipton conceded, are very different from secondary hormonal agents and have very different side effects. JFF 965-967. And Defendants have provided no evidence that Jevtana's use with prednisone was known in the prior art.

would be therapeutically effective against advanced prostate cancer, especially when combined with abiraterone. *See supra* at 23-27. Defendants' failure to make any effort to establish a reasonable expectation of achieving *what is claimed* by the '438 patent is reason enough to reject their obviousness challenge.

C. Defendants Cannot Establish Clear and Convincing Evidence that the Dependent Claims are Obvious.

Defendants' obviousness arguments with regard to the dependent claims at issue fare worse than those on the independent claims. Defendants made no argument at trial or in their post-trial briefs that administering abiraterone plus prednisone to patients who are refractory to docetaxel, as required by claim 20, would have been obvious. Defendants therefore failed to meet their burden of proof with respect to claim 20.

Defendants argue that the 1000 mg/day of abiraterone in the dependent claims would have been obvious in view of O'Donnell 2004, which supposedly taught that 800 mg/day successfully suppresses testosterone levels to castrate range. Defs. Br. 53. But Defendants cite no testimony by any expert to support this. Attorney argument cannot be clear and convincing evidence. Moreover, in O'Donnell 2004, abiraterone failed to achieve sustained testosterone suppression at the doses tested, and a skilled artisan in 2006 would not have known whether increasing doses would result in sustained suppression, much less anti-cancer activity. JFF 771-772.

Defendants argue that the 10 mg/day of prednisone in the dependent claims would also have been obvious in view of Gerber, Tannock 1996, and the use of 10 mg as glucocorticoid replacement. Defs. Br. 53. However, Defendants provide no evidence that a skilled person would expect the doses disclosed in these references to be effective for treating prostate cancer. Further, Sartor 1998 taught the use of 20 mg/day of prednisone and stated that "the percentage of

patients with PSA declines is higher in patients receiving higher doses of glucocorticoids," teaching away from using lower doses of prednisone. DTX1087.1; JFF 810-811.

D. Defendants Fail to Overcome the Objective Indicia Confirming that the '438 Patent Is Not Obvious.

Janssen's post-trial brief demonstrated that each of the objective indicia confirms the asserted claims of the '438 patent are not obvious. Janssen Br. 59-66; *see also Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378-79 (Fed. Cir. 2012) (objective indicia "may often establish that an invention appearing to have been obvious … was not"). Defendants quibble but have no real response to the fact that by any real-world measure, the '438 patent was not obvious.

a. ZYTIGA Has Been A Commercial Success.

ZYTIGA's extraordinary commercial success, which is directly linked to the invention claimed by the '438 patent, confirms that the asserted claims are not obvious. Janssen Br. 58-61. Defendants do not dispute that ZYTIGA plus prednisone is a blockbuster therapy with over five-billion in sales and a substantial market share. And the attacks they do make are unavailing.

Defendants' primary argument is that the '213 patent is a "blocking patent" that precludes a finding of commercial success. Defs. Br. 59-60. Of course, the existence of a blocking patent is not dispositive. *See Acorda Therapeutics, Inc. v. Roxane Labs, Inc.*, 2018 WL 42888982, at *20 (Fed. Cir. Sept. 10, 2018) ("magnitude" of effect "is 'a fact-specific inquiry'"). Defendants assert that the '213 patent is a blocking patent because it was exclusively licensed to Cougar from April 20, 2004 through the priority date of the '438 patent. *Id.* at 59. But neither Defendants nor their expert, Mr. Hofmann, offered a justification for focusing on the period between Cougar's exclusive license and August 2006. Janssen Br. 61; Defs. Br. 60. The purpose of the commercial success analysis is that a valuable invention would have been discovered and brought to market sooner if it were obvious. Tr. 1787:10-1788:3; Tr. 2059:2-12. Mr. Hofmann's

analysis contradicts this basic framework by focusing exclusively on the period in which Cougar held an exclusive license, while disregarding the important years beforehand when other companies failed to discover the invention despite opportunities to do so. Tr. 1819:25-1820:9.

Defendants attack Dr. Vellturo's testimony, Defs. Br. 60, but they largely ignore his analysis in favor of cherry-picking quotations. Dr. Vellturo explained that "[d]uring the period from 1999 to April 2004," when BTG actively shopped the '213 patent, that patent "clearly was not a blocking patent." Tr. 1828:12-17; 1820:23-1821:7. He further explained that even after Cougar obtained an exclusive license in April 2004, means existed for other companies to access the '213 patent, such as by acquiring Cougar, Tr. 1825:16-1826:11, 1828:12-17, which Janssen's parent, J&J, did in May 2009, Tr. 2046:18-21.[27]

Once the inquiry is focused on the proper time frame, Defendants have no argument, effectively acknowledging that the '213 patent was not a blocking patent from Boehringer's withdrawal in 1999 until Cougar's license in April 2004.[28] Defendants try to undermine Dr. Judson's testimony, contending that he was not personally involved in BTG's licensing efforts. Defs. Br. 60. However, as he explained at trial, Dr. Judson presented data from the O'Donnell study to pharmaceutical companies as part of BTG's efforts to license the '213 patent. Tr. 229:3-230:17; JFF 1042. And he was informed of BTG's licensing efforts by Roger Harrison, a BTG executive. Tr. 229:3-9. Defendants' attack also ignores BTG's website, which shows that BTG was attempting to license the '213 patent. JFF 1043.

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[27] Defendants claim that the period after Cougar's April 2004 license is significant because O'Donnell 2004 was not publicly available until May 2004. Defs. Br. 59-60. But the publication date of O'Donnell 2004 has no special significance. BTG's website promoted the O'Donnell trial results years before O'Donnell was published as part of its efforts to license the '213 patent. JFF 1043. And Dr. Judson presented the O'Donnell data to potential licensees. JFF 1042.

[28] This evidence distinguishes this case from *Acorda* in which there was "no evidence that Elan sought to license the Elan patent to any entity other than Acorda." 2018 WL 42888982, at *20.

Defendants also try to challenge the nexus between ZYTIGA's success and the '438 patent. Specifically, Defendants contend that Janssen does not sell prednisone with ZYTIGA and that Dr. Vellturo did not determine how much demand is due to abiraterone versus prednisone. Defs. Br. 60-61. But this misses the mark. "It is not necessary … that the patented invention be solely responsible for the commercial success." *Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991). And Janssen demonstrated at trial that the extension study drove its clinical program, and that prednisone contributes to the efficacy of the combination. Janssen also established that the '438 patent covers the use of ZYTIGA plus prednisone, which shifts the burden to Defendants to show that ZYTIGA's success is due to factors other than the claimed invention. *JT Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). Defendants, however, offered no evidence that demand for ZYTIGA is driven solely by something other than the anti-cancer benefit of the combination of abiraterone and prednisone.

Defendants' argument really amounts to an attack on Janssen's infringement proof that prednisone contributes to the anti-cancer effect of the combination. If this Court finds (as it should) that prednisone provides an anti-cancer benefit when combined with abiraterone, then the commercial success of ZYTIGA plus prednisone confirms that the asserted claims are not obvious. Given the large reward available, if it were obvious to pursue abiraterone and to then combine it with prednisone to solve the long felt need for an effective treatment for advanced prostate cancer, someone would have done this long before the '438 patent inventors.

b. Failure of Others Supports Non-Obviousness.

The failure of others to develop a better prostate cancer treatment similarly reinforces the conclusion that the '438 patent is not obvious. Janssen Br. 62. Defendants do not contest that many investigatory compounds did not demonstrate a survival advantage, whereas the patented combination did. Instead, they contend that these failures are irrelevant. Defs. Br. 64. But

Defendants are wrong. "[T]he failure of others to develop a safe and effective drug often supports the non-obviousness of a drug that finally achieves success." *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 876 F. Supp. 2d 295, 417 (S.D.N.Y. 2012), *aff'd in relevant part*, 723 F.3d 1363 (Fed. Cir. 2013); *see also Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1054 (Fed. Cir. 1988) ("the failure of others to provide a feasible solution to a long standing problem is probative of nonobviousness.").

Even on their own terms, Defendants are mistaken. Abiraterone was not "always a success when tested." In O'Donnell 2004, abiraterone failed to achieve sustained testosterone suppression. JFF 767-771, 774. And, after the O'Donnell study was completed in 1999, Boehringer abandoned abiraterone, which sat on the shelf at BTG, while BTG struggled to find a licensee and the O'Donnell authors remained unpublished. JFF 777-790, 1029-1049, 1071-74.

c. Skepticism Supports Non-Obviousness.

Non-obviousness of the asserted claims is also confirmed by the considerable skepticism of the invention claimed by the '438 patent. Janssen Br. 62-63. Defendants do not address the general skepticism of second-line hormonal therapies or the advice from Dr. de Bono's mentor that he was wasting his time studying abiraterone. JFF 756, 1059-60, 1064. They also do not address the skepticism of Dr. de Bono's proposal to combine abiraterone with a glucocorticoid even among colleagues on Cougar's scientific advisory board. JFF 1065-66.

Defendants contend that the fact O'Donnell "was rejected by a journal or two says nothing" because that is a normal part of publishing. Defs. Br. 62-63. But O'Donnell was rejected by at least three different journals and the results took over five years to get published, which is unusual. JFF 1061. Dr. Bantle acknowledged that it was unusual for a manuscript to take this long to be accepted for publication. *Id.* Moreover, Defendants avoid addressing the reviewer comments on the rejected draft of the O'Donnell paper, which were skeptical of the

usefulness of adrenal steroid inhibitors like abiraterone. JFF 1062-1063; JTX 8064 at 2. Defendants say that skepticism about abiraterone is irrelevant, Defs. Br. 63, but this ignores that skepticism about abiraterone or secondary-hormonal therapies necessarily means skepticism toward abiraterone plus prednisone.

Defendants also argue that Boehringer's decision to stop developing abiraterone, and BTG's difficulties in licensing it, do not show skepticism because no one knows why Boehringer withdrew support or companies refused a license. Defs. Br. 63-64. But the unrebutted evidence is that Boehringer stopped its involvement with abiraterone after the O'Donnell trials were completed in 1999. JFF 1031-1034. And BTG could not find another licensee for five years while shopping and promoting the O'Donnell data. JFF 1037, 1042-1045, 1073. If it were obvious to pursue abiraterone after the O'Donnell study to meet the long felt need (and thereby create a blockbuster drug), surely Boehringer and the other pharmaceutical companies would have jumped at the opportunity.

d. Long Felt but Unmet Need Supports Obviousness.

Defendants also fail to rebut the evidence that in 2006 there was a pressing need for an alternative to the toxic chemotherapy agent docetaxel, and that abiraterone plus prednisone provided that superior alternative after decades of failure with secondary-hormonal therapies. Janssen Br. 63. Defendants claim that the long-felt need was met when abiraterone was discovered and patented. Defs. Br. 64. However, the '213 patent on abiraterone issued in 1997. By 2006 the only therapy available to mCRPC patients that improved survival was the problematic chemotherapy docetaxel. JFF 1077.

e. Unexpected Results Support Obviousness.

The unexpected results of the '438 patent invention also reinforce nonobviousness. Janssen Br. 62. Defendants have no response to the fact that the extension study established an

"unprecedented" outcome when drugs that had failed when administered on their own were successful when combined together. JFF 116-146, 1051-1055. Defendants contend that there were no unexpected results because prednisone has not been proven to have anti-cancer effects with abiraterone. Defs. Br. 62. As shown, Defendants are wrong. *See supra* at 2-10.

Defendants also argue that any unexpected results "are simply a difference in degree, and not in kind." Defs. Br. 62. This is premised on the erroneous assumption that improved efficacy over alternative therapies, no matter how significant or surprising, is just a difference in degree. However, courts have often found that substantial and unexpected improvements in efficacy establish unexpected results. *See Proctor & Gamble Co. v. Teva Pharm. USA, Inc.*, 536 F. Supp. 2d 476, 495-96 (D. Del. 2008) (three-time improvement was "unexpected"); *Daiichi Sankyo Co. v. Mylan Pharm. Inc.*, 670 F. Supp. 2d 359, 382-83 (D.N.J. 2009) (two to three fold improvement unexpected), *aff'd*, 619 F.3d 1346 (Fed. Cir. 2010). *Galderma Laboratories, L.P. v. Tolmar, Inc.*, upon which Defendants rely, does not support their assertion. It merely held that "where an unexpected increase in efficacy is measured by *a small percentage* … the result constitutes a difference in degree, not kind." 737 F.3d 731, 739 (Fed. Cir. 2013). And here, the increase in efficacy is not a small percentage.

Two drugs that had failed individually should not have worked at all, much less produced a considerable survival benefit. Janssen Br. 64; JFF 734-744, 751-762. Xu 2015 shows that TTPP is "highly associated" with overall survival in patients treated with abiraterone plus prednisone. JFF 214-219. And Dr. Rettig's cross-study comparison showed that abiraterone plus prednisone more than doubled the TTPP of abiraterone alone, from 7.5 months to 16.3 months. JFF 220-222, 1056. Use of the combination provides not only unexpectedly enhanced TTPP, but also overall survival. JFF 1057-58. Defendants compare abiraterone plus prednisone to

docetaxel and Jevtana, but even that comparison shows considerable and unexpected improvements in efficacy.[29] The COU-AA-302 study, for instance, demonstrated a median survival benefit of 4.4 months in mCRPC patients, a 76% improvement compared to docetaxel. JFF 351-359, 763, 1057. That is no "small percentage," particularly for patients with advanced prostate cancer.

f. Professional Approval and Industry Praise Support Obviousness.

Finally, professional approval and industry praise support a finding of non-obviousness of the asserted claims. Janssen Br. 65. Defendants attack the evidence of praise based on conclusory assertions of Dr. Lipton, who dismissed all evidence of praise based on the notion that prednisone does not have anti-cancer effects with abiraterone. *See* Defs. Br. 64-65; DFF 618 (citing Lipton). But Dr. Lipton's testimony is "lacking in detail and lacking support in the record." *Norgen Inc. v. Int'l Trade Comm'n*, 699 F.3d 1317, 1327 (Fed. Cir. 2012).

Defendants also claim that there is no evidence of praise for Dr. de Bono's reversal of resistance hypothesis, but they ignore the numerous peer-reviewed publications recognizing it. JFF 154-162, 164, 167-182. Defendants also have no response to the praise for the COU-AA-301, COU-AA-302, and LATITUDE studies of the combination therapy; these were recognized through publication in, for example, the *New England Journal of Medicine*, and they changed medical practice. JFF 347-348, 353-354, 356-358, 365, 369-371, 1081-1082, 1086-1087.

E. Defendants' Attack on Dr. de Bono Is Meritless.

As the inventor of the '438 patent, Dr. de Bono testified about the process that led to his invention. Defendants now contend that his testimony should be excluded because he

[29] Jevtana and docetaxel are chemotherapies with significantly different mechanisms of action and side effects. JFF 966-967, 1077-1078. Defendants themselves have argued that the closest prior art is abiraterone by itself, not docetaxel or Jevtana. DFF 504. Nonetheless, the patented invention shows considerable improvements over these.

supposedly offered undisclosed expert testimony by testifying about the state of the art at the time, practices surrounding clinical trials, and the import of prior art. Defs. Br. 66. Defendants' challenge is meritless.

"When a lay witness has particularized knowledge by virtue of her experience, she may testify—even if the subject matter is specialized or technical—because the testimony is based upon the layperson's personal knowledge rather than on specialized knowledge within the scope of [Federal Rule of Evidence] 702." *Donlin v. Philips Lighting N. Am. Corp.*, 581 F.3d 73, 81 (3d Cir. 2009). Accordingly, courts routinely allow inventors to testify concerning prior art and related technical knowledge. *See In re Omeprazole Patent Litig.*, 2002 WL 287785, at *6 n.7 (S.D.N.Y. Feb. 27, 2002) ("[F]act witnesses who are skilled in the art, including the named inventors of the [patents-in-suit], are competent to testify concerning prior art documents."); *Supernus Pharm., Inc. v. Twi Pharm., Inc.*, 265 F. Supp. 3d 490, 517 n.12 (D.N.J. 2017) (denying motion to exclude inventor's testimony "as improperly disclosed expert testimony" where "he properly testified as to matters which, while technical and specialized, are squarely within his particularized firsthand knowledge and experience … as an inventor on the Patents-in-Suit").[30]

F. Defendants' Reliance on IPR Proceedings and Final Written Decisions Is Inappropriate.

Throughout their brief, Defendants rely on the PTAB's Final Written Decisions as supposed evidence to support its invalidity challenge. This is inappropriate, and those decisions should be excluded. Janssen Br. 67-68. The PTAB applies a different standard of proof, and

[30] *See also Skyhook Wireless, Inc. v. Google, Inc.*, 2015 WL 10015295, at *3 (D. Mass. Feb. 27, 2015) (inventor would testify only to "first-hand knowledge" of such topics as "the invention story" of the patents-in-suit); *CIVIX-DDI, LLC v. Hotels.com LP*, 2012 WL 6591684, at *4 (N.D. Ill. Dec. 18, 2012); *Knowles Elec., LLC v. Microtronic U.S., Inc.*, 2000 WL 310305, at *2 (N.D. Ill. Mar. 24, 2000).

lacked the broader discovery and live cross-examination that will inform this Court's decision. Indeed, Defendants' reliance on the PTAB is particularly unseemly given their insistence that this Court should resolve the obviousness defense notwithstanding the PTAB's earlier decisions and § 315(e)(2). *Id.* at 66-67.

IV. The '438 Patent Does Not Lack a Written Description.

The specification of the '438 patent more than satisfies the written description requirement. Janssen Br. 68-69. The specification informs one skilled in the art that prednisone provides an anti-cancer effect in combination with abiraterone, at the claimed doses, as the claims require. *Id.* Defendants have failed to show otherwise by clear and convincing evidence.

Defendants' primary argument is that written description is lacking because the specification contains "no test results … or any other data," "no mention or explanation of Dr. de Bono's reversal of resistance theory," or any "prophetic example." Defs. Br. 68. But, as Janssen explained, "[t]here is no requirement that the disclosure contain 'either examples or an actual reduction to practice.'" *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014); Janssen Br. 68. Written description "is *not* about whether the patentee has proven to the skilled reader that the invention works, or how to make it work, which is an enablement issue." *Alcon*, 745 F.3d at 1191. The proper inquiry is whether the specification provides an adequate description to one skilled in the art "to visualize or recognize the identity of the subject matter purportedly described." *Id.* at 1190. The specification of the '438 patent provides a sufficient description of the invention to one skilled in the art, including the anti-cancer effect of prednisone. Janssen Br. 68-69. This is so even though the specification does not have to describe the benefit of prednisone, which is an inherent property of the formulations described in the specification. Janssen Br. 69. Defendants say nothing about this.

Defendants make much of the fact that the prior art did not teach prednisone's anti-cancer

effects, Defs. Br. 67,[31] but written description does not rely on what the prior art taught; it focuses solely on what the specification discloses, and here the specification discloses the invention in a definite way to one skilled in the art. *See Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1308 (Fed. Cir. 2015). Defendants contend that the specification refers to prednisone as an antibiotic agent or steroid, rather than as an anti-cancer agent. Defs. Br. 68. But this Court has already found that the specification in "the '438 patent throughout refers only to anti-cancer effects." JFF 1098. Thus, the specification teaches that prednisone is used to treat cancer with abiraterone, whether it is characterized as a steroid or another agent. Janssen Br. 68-69; JFF 1090-1097.

Defendants err in suggesting that *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002), supports their argument. Defs. Br. 69. In *Enzo*, the Federal Circuit merely rejected the argument that written description "is necessarily met as a matter of law" when the claim language appears verbatim in the specification. 323 F.3d at 968. It did nothing to alter *Alcon* or *Allergan* and, in fact, reaffirmed that written description is "a fact-based inquiry that will necessarily vary depending on the nature of the invention claimed." *Id.* at 963. As explained, the specification here sufficiently describes the claimed method of treatment. Janssen Br. 68-69.

CONCLUSION

For the foregoing reasons, and those in Janssen's Post-Trial Brief, the Court should find the '438 patent not invalid and infringed by Defendants.

[31] Defendants contend that the "-001 dexamethasone extension study … had not begun recruiting patients" as of August 2006, Defs. Br. 69. However, COU-AA-001 EXT, on which Defendants rely, is not the extension study in which Dr. de Bono administered dexamethasone. That was COU-AA-001 itself, which began enrolling patients in November 2005. JTX 8142 at 1-3.

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CERTIFICATE OF SERVICE

I hereby certify that on September 21, 2018, copies of the foregoing Post-Trial Response Brief were electronically filed and served by notice of electronic filing upon all counsel of record.

Dated: September 21, 2018

/s/ Keith J. Miller
Keith J. Miller